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(54) Title of the Invention: SUSTAINED RELEASE PREPARATION FOR COMPOSITION AND ITS
MANUFACTURING METHOD

A composition for sustained release drugs and the manufacturing process

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Specification

1. Title of the Invention

SUSTAINED RELEASE PREPARATION FOR COMPOSITION AND ITS
MANUFACTURING METHOD

2. Scope of Claims for Patents

(1) A sustained release preparation for the composition comprising of crystalline poor solubility basic drug and its salt and, 0.3 – 16 parts by weight higher fatty acid, 0.3 – 16 parts by weight enteric polymer and 0.002 – 2 parts by weight surfactant for crystalline poor solubility basic drug and its salt.

(2) The higher fatty acid in the sustained release preparation for the composition according to Claim (1) is 12 – 18 higher fatty acids.

(3) The enteric polymer in the sustained release preparation for the composition according to Claims (1) and (2) is more than 1 or 2 types of enteric polymers selected from methacrylic acid - methacrylic acid ester copolymer, methacrylic acid - acrylic acid ester copolymer, cellulose succinates, cellulose phthalates and carboxymethyl celluloses.

(4) The surfactant in the sustained release preparation for the composition according to any of Claims (1) – (3) is a non-ionic surfactant.

(5) The crystalline poor solubility basic drug and its salt in the sustained release preparation for the composition according to any of Claims (1) – (4) is a crystalline nicardipine.

(6) The dosage forms of the sustained release preparation for the composition according to any of Claims (1) – (5) are pellets, fine granules and capsules.

(7) A method for manufacturing the sustained release preparation for the composition by means of crushing, followed by granulating the crystalline poor

solubility basic drug and its salt after kneading it with 0.3 – 16 parts by weight higher fatty acid, 0.3 – 16 parts by weight enteric polymer and 0.002 – 2 parts by weight surfactant for crystalline poor solubility basic drug and its salt.

(8) The higher fatty acid in the method for manufacturing the sustained release preparation for the composition according to Claim (7) is carbon number 12 – 18 higher fatty acids.

(9) The enteric polymer in the method for manufacturing the sustained release preparation for the composition according to Claims (7) and (8) is more than 1 or 2 types of enteric polymers selected from methacrylic acid - methacrylic acid ester copolymer, methacrylic acid - acrylic acid ester copolymer, cellulose succinates, cellulose phthalates and carboxymethyl celluloses.

(10) The surfactant in the method for manufacturing the sustained release preparation for the composition according to any of Claims (7) – (9) is a non-ionic surfactant.

(11) The crystalline poor solubility basic drug and its salt in the method for manufacturing the sustained release preparation for the composition according to any of Claims (7) – (10) is a crystalline nicardipine.

(12) The dosage forms of the sustained release preparation for the composition in the method for manufacturing the sustained release preparation for the composition according to any of Claims (7) – (11) are pellets, fine granules and capsules.

3. Detailed Description of the Invention

[Industrial Applicability]

The present invention relates to the sustained release preparation for the composition of a poorly soluble basic drug, for which the sustained release preparation is difficult since the drug's solubility in the intestine is very low, salt present, and its simple manufacturing method. Therefore, the object of the present invention is to provide the sustained release preparation made from the poorly crystalline soluble basic drug or its salt, higher fatty acid, enteric polymer and surface activating agent, and its simple manufacturing method.

[Conventional Technology]

The poorly soluble basic drug with very low solubility in the intestine, and its salt are ill-suited for using them as it is, in the sustained release preparation. Further, many documents have been widely known to solve these problems. For example, in Japanese Patent Laid-Open No. 59-48810, one of the poorly soluble basic drugs, nicardipine is amorphized using ball mill crushing or vibration ball mill crushing and the sustained composition with improved intestinal absorption is described. In Japanese Patent Laid-Open No. 56-49314, 58-116414 and 63-174929, a sustained release preparation is described which includes amorphous nicardipine wherein spray drying, adsorption or coating in presence of the carrier, after adding a certain polymer material to an organic solvent solution of Nicardipine, is carried out. Any of the aforementioned are characterized in using the nicardipine after its amorphization.

It is known the amorphous nicardipine, which is assumed as one of the poorly soluble basic drugs, can be used in the sustained release preparation in this manner.

[Problem to be Solved by the Invention]

However, in general, problems may arise for long term physical stability, complexity and economy of the manufacturing in the preparation consisting of the amorphized pharmacological agents as a whole. More specifically, the manufacturing of amorphized nicardipine is extremely complicated wherein the problems such as the change in the solubility and stability of pharmacological agents due to crystallization of pharmacological agents may arise. For example, when the amorphization is carried out using ball mill crushing, since the collision of the ball and the crystals is the rate controlling step of the amorphization, it requires a fairly longer period of time wherein the residual crystals may become the seed crystals and there is a possibility of crystallization. In addition, when the amorphization is carried out using the solvent removal method, it is complicated and uneconomical since it requires a drying process which needs a longer period of time for reducing the residual solvent in the product, besides requiring consideration of environmental pollution due to the removed solvent as well. Further, the polymers compatible with the pharmacological agents are routinely added several times to measure the sustention of the amorphous state for a longer period of time; as a result, it also has some demerits such as the unnecessary increase in the size of the preparation. Still further, various additives are added to the amorphous nicardipine preparation in order to have an appropriate controlled release of the pharmacological agents; however, many of these are the polymers which are traditionally used in the medical preparation field and usually have moisture content. It is a well-known fact for people skilled in the art that the moisture will have a great impact on the chemical stability of the amorphous compound and sustention of the amorphous state.

[Means for Solving the Problem]

As a result of extensive studies carried out by the inventors of the present invention to resolve the demerits of the conventional techniques, it was determined the composition for the sustained release preparation of the poorly soluble basic drug with excellent sustained release and stability can be obtained very easily by kneading the poorly soluble basic drug and its salt, and 0.3~16 higher fatty acid, 0.3~16 enteric polymer and 0.002~2 of surface acting agents by the respective ratios by weight for the poorly crystallized soluble basic drugs and its salt together, followed by grinding and granulating it, and the present invention can be accomplished thereof.

Next, the present invention will be described in detail.

The poorly crystallized soluble basic drug of the present invention has 0.1~300 µg/ml solubility for the artificial intestinal juice (Japanese Pharmacopoeia 11th Amendment, No. 2 liquid described in the disintegration test) of free base or its acid addition salt, wherein it signifies the pharmacological agents consisting of the basic group which forms the acid addition salts; for example, crystallized nicardipine, dibuildamol, diltiazem, diazepam, ketotifen, disopyramide, chlorpheniramine, diphenhydramine and the like can be cited. For the acids which forms the acid addition salt, there is no restriction in particular if the acid is pharmaceutically acceptable, for example inorganic acids such as sulphate oxide, phosphoric acid and the like, sulphonic acids such as methanesulphonic acid, p-toluenesulphonic acid and the like, and organic acids such as citric acid, fumaric acid, maleic acid and the like can be cited. Further, structurally it is an amphoteric substance; however, the acidic dissociation constant is less, and it shows properties for the base. The present invention can be applied to the pharmacological agent with the solubility from 0.1 to 300 µg/ml for the artificial

intestinal juice (no. 2 liquid described in the disintegration test method as per Japanese Pharmacopoeia 11th Amendment) of the acid addition salts and amphoteric substances I intestinal juice; for example, pharmacological agent pyridine carbon acid such as tosulfoxacin.

All of the higher fatty acids of carbon numbers 12~22 can be used as the higher fatty acids used in the present invention, for example, straight chain saturated fatty acids, straight chain unsaturated fatty acids, oxy fatty acids, branched chain fatty acids and the like can be cited, and further, it is acceptable to use the acid of one type or two types combined together as per requirement. Specifically, for example, lauric acid, myristic acid palmitic acid stearic acid, arachic acid, behenic acid and the like can be cited as the straight chain saturated fatty acids; for example dodecene acid, myristoleic acid, palmitoleic acid, oleic acid, linoleic acid, eicosenoic acid, blubber oil acid, eicosapentaenoic acid and the like can be cited as the straight chain unsaturated fatty acids; for example, linoleic acid, dioystearic acid and the like can be cited as the oxy fatty acids whereas for example, methylpalmitic acid and the like can be cited as the branched chain fatty acids. Of the higher fatty acids, the higher fatty acids of solid carbon numbers 12~18 at room temperature are preferable.

For example, methacrylic acid-methacrylic acid ester copolymer, methacrylic acid-acrylic acid ester copolymer, cellulose succinate group, cellulose phthalate group, carboxydimethyl cellulose class and the like can be cited as the enteric polymer used in the present invention; further, it is acceptable to use the acid of one type or two types combined together as per requirement. Specifically, for example, methacrylic acid-methacryl acid methyl copolymer(Product name: Eudragit S-100) and the like can be cited as methacrylic acid-methacrylic acid ester copolymer; for example methacryl acid-acrylic acid methyl copolymer (Product name: Eudragit L-100) and methacrylic acid-acrylic acid ethyl copolymer (Product name: Eudragit L-100-55) (All the above Made by Rohm and Hass Co.) and the like can be cited as the methacrylic acid-acrylic acid ester copolymer; for example, hydroxypropyl methylcellulose acetate succinate (Product name: AQOAT) can be cited as the cellulose succinate group; for example, hydroxypropyl methylcellulose phthalate (Product name:HP-55 and HP-50) (all the above made by Shinetsu Chemicals) can be cited as the cellulose phthalate group; for example, carboxydimethyl ethyl cellulose [Product name: CMEC (Made by Freund Industries)] can be cited as the carboxydimethyl cellulose group. The anionic, non-ionic, cationic and dipolar surface acting agents can be cited as the surface acting agents used in the present invention; further, it is acceptable to use the acid of one type or two types combined together as per requirement. Specifically, for example, sodium lauryl sulphate (Product name: NIKKOL SLS), polyoxyethylene (10) sodium lauryl ether phosphate (Product name: NIKKOL DLP-10) (all of the above are made by Nikko Chemicals) and the like can be cited as the anionic surface activating agents; for example, polyoxyethylene (40) monostearate (Product name: NIKKOL MYS-40), polyoxyethylene (9) laurylether (Product name: NIKKOL BL-9EX), polyoxyethylene (20) sorbitan monooleate (Product name: NIKKOL T0-10) (all of the above are made by NIKKO chemicals), polyoxyethylene (105) polyoxypropylene (5) glycol [Product name: PEP101 (Made by Freund Industries Ltd.) and the like can be cited as the non-ionic surface activating agents; for example, stearic acid ammonium chloride [Product name: NIKKOL CA-2465 (Made by Nikko Chemicals)] and the like can be cited as the methyl ammonium cations surface activating agents whereas for example, lecithin,

lauryl methyl aminobetain [Product name: NIKKOL AM-301 (Made by Nikko Chemicals)] and the like can be cited as the surface activating agents. Of these surface activating agents, non-ionic surface activating agents are preferable.

Next, the method for manufacturing the sustained release preparation for the composition of the present invention will be described.

The example of the manufacturing method given as an ideal example of the present invention obtains the sustained release preparation by carrying out grinding and granulation known in the relevant field, after the ground poorly soluble drug and its salt, and 0.3~16 higher fatty acids, 0.3~16 enteric polymer and 0.002~2 surface activation agents are kneaded with the respective ratios by weight for the poorly crystallized soluble basic drug and its salt. In such a situation, the example which is manufactured by using the higher fatty acids of solid carbon numbers 12~18 at room temperature, by heating up the poorly crystallized soluble basic drug or its salt, relevant higher fatty acids, enteric polymer and surface activating agent at the temperature near the melting point of relevant higher fatty acids, kneading the mixture after melting, cooling and solidifying the same, followed by grinding and granulating, can be cited as the preferred example. Further, the sustained release preparation can also be obtained by breaking the overall composition to the desired grain size in advance, heating up under the rolling state and softening and melting the higher fatty acid.

When the higher fatty acids are in an aqueous fluid form at room temperature, the composition for sustained release preparation can be obtained by carrying out solidification after adding a diluting agent of oil absorption such as light anhydrous silicic acid and the like.

Note that, the grinding of the poorly crystallized soluble basic drug and its salt is carried out to prevent the incorporation of the large particles wherein particularly fine grinding is not necessary and the normal size achieved using the hammer type grinder is acceptable.

Further, to grind after cooling, a grinder mill, tornado mill, flash mill and the like which are generally utilized, can be used for the purpose of granulating.

Next the quantity will be described.

The compounding ratio described below indicates the ratio by weight of the relevant composition accounting for the overall composition.

The quantity of the poorly crystallized soluble basic drug and its salt can be selected arbitrarily by combining according to the efficacy expression level and solubility of the pharmacological agents wherein, usually the ratio by weight for the entire preparation is 5~50% whereas 10~30% is preferable.

The quantity of higher fatty acids and enteric polymer higher fatty acids is 0.3~16 ratio by weight respectively for the poorly crystallized soluble basic drug and its salt, wherein preferably it should be 1~5 respectively. It is even more preferable, if the higher fatty acids are used more than the enteric polymers, since the deterioration in the dissolution in the No.2 liquid described in the disintegration test method of Japanese Pharmacopoeia 11th Amendment, and fixing of particles after granulation are observed; generally it is preferable to use the higher fatty acids less than the enteric polymers. In addition, when the pharmacological agents have unstable moisture content, the enteric polymers can be dried in advance and then used.

Note that, since the problems such as weakening of the surface activating agent effect may arise in the composition when anionic surface activating agents are

combined with the pharmacological agents of acid addition salt, the combination with the pharmacological agents is arbitrarily selected and then used.

The quantity of surface activating agents is 0.002~2 ratio by weight and preferably 0.016~0.5 ratio by weight for the poorly crystallized soluble basic drug and its salt.

The composition thus obtained can be used as it is or as per requirement, the diluting agents such as lactose and the like, plasticizer such as triethyl citrate and the like, plasticizer such as magnesium stearate and the like, antistatic agents such as magnesium stearate and the like, agents such as citric acid, fumaric acid and the like, used in the composition for sustained release preparation can be added individually or more than 2 as per convention within the range in which they will not affect the sustained release.

There is no restriction in particular for the heating temperature, if the higher fatty acids can be softened or melted and the kneaded state can be achieved, however, normally 40-90°C is assumed as ideal.

The usual equipment such as the kneader or the Henschel mixer and the like can be used as the kneading devices.

The composition for sustained release preparation thus obtained can be conditioned by the conventional methods using any of the usually known formulations; however, for the preferable formulations, granules, subtle granules or the capsules obtained by packing these in the hard gelatine capsules and the like can be cited.

Next, the elution of the poorly soluble basic drug from the composition for the sustained release preparation of the present invention and the tests related to the stability and blood concentration of the composition for the sustained release preparation of the present invention are described.

(1) Dissolution Test

The dissolution test of the composition for the sustained release preparation obtained in Examples 1~13 are carried out by the Badr method (100 rpm) described in the Japanese Pharmacopoeia dissolution test method. Specifically, the composition for the sustained release preparation consisting of 10 mg of nicardipine hydrochloride is added to 800 ml of No. 2 liquid described in Japanese Pharmacopoeia disintegration test method while maintaining 37 ± 0.5°C. The respective sampling is carried out 10 minutes, 30 minutes, 1 hour, 2 hours and 3 hours after adding. The sampling liquid is passed through the membrane filter (0.3 µm). After sorting 1 ml of solution, quantitative estimation of nicardipine hydrochloride content is carried out by the high performance liquid chromatography (HPLC) method and the dissolution rate is obtained. The results are shown in Figs. 1 to Fig. 3

(2) Stability Test

The stability test is carried out for the composition for sustained release preparation of Example 1 under the conditions shown in Table 1.

Table 1
1-month test results (survival rate of nicardipine)

Test conditions	40°C, Relative humidity 75%	60°C
composition for sustained release preparation of Example 1	98.6%	99.0%

(3) Beagle Dogs Oral Administration Test

3 beagle dogs (boar, body weight 9~10 kg) of 1 group are used, and capsules packed with specimen sustained release preparation are orally administered after overnight fasting. After 1, 2, 4, 6 and 8 hours of administration, respective blood sampling is carried out using the forelimb vein, the quantitative estimation of nicardipine hydrochloride content is carried out using the high performance liquid chromatography (HPLC) method and the serum level of nicardipine is obtained.

The results are shown in Fig. 4.

Note that, 200 mg/subject of nicardipine hydrochloride is administered for the composition of the sustained release preparation of Example 1 and 100 mg/subject of nicardipine hydrochloride is administered for the composition of the sustained release preparation of Examples 2, 5 and 7.

From these results, it is clear the composition of the present invention has excellent dissolution in the artificial intestinal juice and extremely good stability, even further it maintains the serum concentration of stable pharmacological agents for a longer period of time and excels as the composition for the sustained release preparation.

[Examples]

Next, the present invention is described further in the details using the Examples; however, the present invention is not restricted to these.

Note that, the product name is used in the examples; however, the general name of the same is as described below.

Enteric polymer:

HP-55: Hydroxypropylmethyl cellulose phthalate (Made by Shinetsu Chemicals Co.)

AQOAT: Hydroxypropylmethyl cellulose acetate succinate (Made by Shinetsu Chemicals Co.)

CMEC: Carboxymethylethyl cellulose (Made by Freund Industries Ltd.)

Eudragit L-100: Methacrylic acid-acrylic acid methyl copolymer (Made by Rohm and Hass Co.)

Surface activating agent:

NIKKOLMYS-40: Polyoxyethylene (40) monostearate (Made by Nikko Chemicals Co.)

NIKKOLTO-10: Polyoxyethylene (20) Sorbitan monooleate (Nikko Chemicals)

NIKKOLBL-9EX: Polyoxyethylene (9) lauryl ether (Made by Nikko Chemicals Co.)

Example 1

4 g of nicardipine hydrochloride, 7 g of stearic acid, 0.5 of NIKKOLMYS-40 and 8.5 g of HP-55, and sieved using 83 mesh screen, are mixed together so as to make a uniform mixture. Next, the mixture is heated up to approximately 80°C and kneaded under the contact solution of stearic acid. After cooling and solidifying, it is crushed, sieved at 30 mesh screen, and the composition of sustained release preparation of the size fixed on the screen with 83 mesh, is obtained.

Example 2

As the enteric polymer, 8.5 g of Eudragit L-100 is used in place of 8.5 g of HP-55 of Example 1, the operation is carried out similar to Example 1 and the composition for sustained release preparation is obtained.

Example 3

As the higher fatty acid, 7 g of lauric acid is used in place of 7 g of stearic acid of Example 2, then it is heated up to approximately 50°C, the operation is carried out similar to Example 2 and the composition for sustained release preparation is obtained.
Example 4

As the higher fatty acid, 7 g of palmitic acid is used in place of 7 g of stearic acid of Example 1, then it is heated up to approximately 70°C, the operation is carried out similar to Example 1 and the composition for sustained release preparation is obtained.

Example 5

As the enteric polymer, 8.5 g of AQOAT is used in place of 8.5 g of HP-55 of Example 1, the operation is carried out similar to Example 1 and the composition for sustained release preparation is obtained.

Example 6

As the enteric polymer, 8.5 g of CMEC is used in place of 8.5 g of HP-55 of Example 1, the operation is carried out similar to Example 1 and the composition for sustained release preparation is obtained.

Example 7

As a surface activating agent, 0.5 g of NIKKOLT0-10 is used in place of 0.5 g of NIKKOLMYS-40 of Example 5, the operation is carried out similar to Example 5 and the composition for sustained release preparation is obtained.

Example 8

As a surface activating agent, 0.5 g of NIKKOLBL-9EX is used in place of 0.5 g of NIKKOLMYS-40 of Example 5, the operation is carried out similar to Example 5 and the composition for sustained release preparation is obtained.

Example 9

Higher fatty acids of Table 5 are added in place of 7 g of stearic acid of Example 2, as the higher fatty acid, further, the enteric polymer and surface activating agents of Table 5 are added, the operation is carried out similar to Example 2 and composition for sustained release preparation of Examples 9~13 shown in Table 5, are obtained respectively.

Table-5

No.	Poorly soluble basic drug	Higher fatty acids	Enteric polymer higher fatty acids	Surface activating agents
Example 9	Nicardipine hydrochloride 4g	Stearic acid 6g	Eudragit L-100 9.5g	NIKKOL MYS- 40 0.5g
Example 10	Nicardipine hydrochloride 4g	Stearic acid 5g	Eudragit L-100 10.5g	NIKKOL MYS- 40 0.5g
Example 11	Nicardipine hydrochloride 4g	Stearic acid 8g	Eudragit L-100 8.5g	NIKKOL MYS- 40 1.0g
Example 12	Nicardipine hydrochloride 4g	Stearic acid 14g	Eudragit L-100 17g	NIKKOL MYS- 40 1.0g
Example 13	Nicardipine hydrochloride 4g	Stearic acid 14g	AQOAT 17g	NIKKOL MYS- 40 1.0g

Effect of the Invention

For the composition for the sustained release preparation of the present invention, since the higher fatty acids which are poorly soluble in water account for a great part of the composition, the problem of stability does not occur for the pharmacological agents as the water and organic solvents are not required for the manufacturing.

In addition, since the complex operations such as the coating and the like are not required, repeatability is high and homogenous results are easily obtained.

Further, according to the manufacturing method of the present invention, there are no demerits for the amorphous operations such as ball mill crushing or the solvent removal method.

4. Brief Description of the Drawings

[Description of the Drawing]

Fig. 1-3 show the results of the elution testing of a composition for a sustained release drug composed of hydrochloric acid nicardipine obtained in Embodiments 1-13

Fig. 4 shows the serum concentration maintenance of nicardipine when beagles were administered a composition for a sustained release drug composed of the hydrochloric acid nicardipine obtained in Embodiments 1, 2, 5, and 7.

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Fig. 1: Results of the elution testing of a composition for a sustained release drug composed of hydrochloric acid nicardipine

- : The composition of Embodiment 1 ▲ : The composition of Embodiment 3
- : The composition of Embodiment 2 ✱ : The composition of Embodiment 4

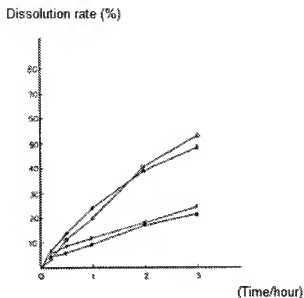


Fig. 2: Results of the elution testing of a composition for sustained release drug composed of hydrochloric acid nicardipine

- ▼ : The composition of Embodiment 5 ▲ : The composition of Embodiment 7
- : The composition of Embodiment 6 ■ : The composition of Embodiment 8

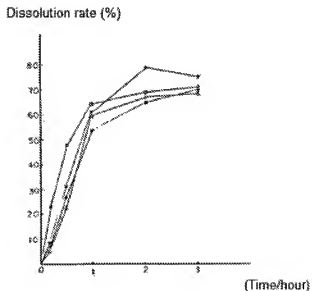


Fig. 3: Results of the elution testing of a composition for sustained release drug composed of hydrochloric acid nicardipine

- ▽ : The composition of Embodiment 9 ■ : The composition of Embodiment 12
 + : The composition of Embodiment 10 ✱ : The composition of Embodiment 4
 ∞ : The composition of Embodiment 11

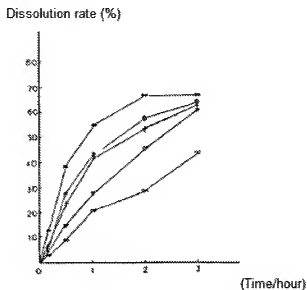


Fig. 4: serum concentration maintenance of the nicardipine with the beagles

- : The composition of Embodiment 1 (administered 200mg/ as hydrochloric acid nicardipine)
 ○ : The composition of Embodiment 2 (administered 100mg/ as hydrochloric acid nicardipine)
 ▼ : The composition of Embodiment 5 (administered 100mg/ as hydrochloric acid nicardipine)
 ▲ : The composition of Embodiment 7 (administered 100mg/ as hydrochloric acid nicardipine)

